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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,492	08/29/2001	Lloyd G. Mitchell	31304-B-A-E 069906.0106	7149

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/941,492	**Applicant(s)** MITCHELL ET AL.	
	Examiner Janet L. Epps-Ford, Ph.D.	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 May 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See item #4*. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-39 remain rejected for the reasons of record in the Office Action mailed 5-05-04*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached note.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: The claim set provided by Applicants, does not comply with 37 CFR 1.121 (c) for the reasons set forth in the attached Notice of Non-Compliant Amendment.

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit: 1635

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 112

2. Claims 1-17 and 35-39 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a chimeric mRNA in a cell *in vitro*, does not reasonably provide enablement for producing a chimeric in a cell *in vivo* for therapeutic treatment of conditions associated with human papilloma virus pre-mRNA expression in a cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in the office action mailed 5-05-04.

3. Applicant's arguments filed 5-24-05 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification clearly discloses actual working examples of transplicing *in vivo,* in particular Applicants make reference to successful in vivo repair of the clotting factor VIII gene using spliceosome-mediated trans-splicing in Example 12. Applicants also argue that the mechanism of splicesosome-mediated trans-splicing to produce a chimeric RNA is the same whether it occurs *in vivo or in vitro.*

In response to Applicant's assertions, Example 12 describes the mouse model of hemophilia, however in the same passage Applicants admit that the molecular basis of human and canine hemophilia associated with factor VIII, involves a more complicated genetic rearrangement in comparison to the mouse model of hemophelia. According to Applicants the

canine model for hemophilia is more closely related to the human system of disease. Therefore, Applicant's own disclosure does not support the conclusion that the mouse model of genetic correction by using the PTMs of the instant invention provides sufficient guidance for the skilled artisan to apply these techniques directly to a human, and produce a therapeutic benefit, without further *de novo* experimentation. Moreover, Applicants do not provide any controls in their experiment, such that the described benefits as set forth in Figure 46 can be fully attributed to actual genetic correction afforded by the administered PTM expression constructs

In response to Applicant's assertions that the mechanism of splicesosome-mediated trans-splicing to produce a chimeric RNA is the same whether it occurs *in vivo or in vitro,* the examiner agrees with Applicants. However, Applicants have not provided a clear correlation between trans-splicing *in vitro* and the production of *in vivo* therapeutic effects. Although the mechanism may be the same, contrary to Applicant's assertions how to deliver the appropriate vectors expressing PTMs to the appropriate tissues, at the appropriate time, for a sufficient duration and concentration to correct a genetic defect and thereby produce a desired therapeutic effect *in vivo* has not been fully established. As stated in the prior Office Action, applicants have not provided any guidance regarding how to overcome the various factors that are known in the art to complicate the gene therapy art, i.e. the expression of the nucleic acid molecules of the invention for therapeutic purposes. As stated in the prior Office Action, "[t]here are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the

genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated." Applicants have not addressed these factors, nor have they discussed how the specification as filed can be used as a guide to overcome these factors.

Again, Applicants argue that recent teachings provide evidence of enablement for the *in vivo* use of PTMs targeted to human papilloma virus (Bhaumik, 2004), Factor VIII (Chao, 2003) and hyper-IgM X-linked immunodifficiency (Tahara et al., 2004). As stated in the prior Office Action, the instant specification claims priority back to 12/15/1995, and at the time the invention was made, the state of the prior art indicated that efficient delivery and expression of foreign DNA was not yet achieved by any method (Marshall, Science, 269:1050-1055, August, 1995). See MPEP § 2164.05 that states "[T]o overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing." At the time of the instant invention the teachings of Bhaumik, Chao, and Tahara et al. was not known the skilled artisan, such that the skilled artisan would have been capable of using (at the time of filing) the claimed compositions and methods for treating a disease in a human comprising the administration of vectors which produce the PTMs of the instant invention. The teachings set forth in the Bhaumik (2004), Chao (2003), and Tahara (2004) references were not incorporated into the body of the specification as originally filed. It remains that the instant claims read on a

method of gene therapy, however Applicants have not provided a sufficient correlation between the *in vitro* production of chimeric RNA molecules using the PTMs of the instant invention, and the production of a therapeutic effect in a human.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single gene is replaced and the desired secondary effect (treating a patient with a disease associated with the expression of the papilloma virus gene) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Double Patenting

4. Claim(s) 1-39 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,013487 in view of Hendricks et al. (US Patent No. 5,580,970 A), for the reasons of record set forth in the prior Office Action.

5. Applicant's arguments filed 5-24-05 have been fully considered but they are not persuasive. First it is noted that Applicant's arguments are incomplete since it does not even

address the double patenting rejection of claims 1-39, to the extent that it is based upon the combination of claims 1-39 of US Patent No. 6,013,487 in view of Hendricks et al. (US patent No. 5,580,970). Applicants traversed the instant rejection on the grounds that the claims of the present invention recite a nucleic acid molecule that comprises one or more targeted binding domains that target binding to a human papilloma virus pre-mRNA expressed within a cell, and the claims of the issued patent are not directed to binding domains that target binding to a human papilloma virus pre-mRNA. This statement does not consider the limitations set forth in claim 1 of US 6,013,487 (US'487), that states "a cell comprising a nucleic acid molecules wherein said nucleic acid molecules comprises: a) one or more target binding domains that target binding of the nucleic acid molecule to a target pre-mRNA.." Contrary to Applicant's assertion, based upon the limitations set forth in issued claim 1, it is clear that the claims of the issued US patent encompass nucleic acids comprising one or targeted binding domains that target binding to premRNA generically. The supporting reference Hendricks et al. is provided as evidence that at the time of the instant invention, the skilled artisan would have been motivated to modify the invention set forth in the issued claims to produce potential chimeric RNA that would potentially function as therapeutics to correct defects associated with papilloma virus mRNA, and thereby further elucidate its role in the development of cervical carcinoma. As stated in the prior Office Action, the claims of the issued US Patent 6,013,487 in view of Hendricks et al. was considered to render obvious the instantly claimed invention. Applicants have not addressed how the combination of these two references renders obvious the instantly claimed invention.

6. Applicants further argued that since the instant application claims priority to the US Patent 6,013,487, there would not be an improper extension of the "right to exclude" granted by

the issuance of the instant application as a patent, and therefore the double patenting rejection should be withdrawn. Contrary to Applicant's assertions, it is noted that the doctrine of nonstatutory double patenting is also in public policy (a policy reflected in the statute) so as to prevent possible harassment by multiple assignees. Applicants have not addressed this portion of the doctrine of nonstatutory double patenting. Therefore, for the above reasons, it remains that the double patenting rejection is still considered appropriate.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Janet L. Epps-Ford